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## **Chinese Skullcap: A Viable Adjunct to Cancer Treatment**

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One of the most respected and utilized herbs in traditional Chinese medicine (TCM) is Chinese skullcap (*scutellaria baicalensis*). Although less popular among Western health practitioners, the bioactive agents (e.g., baicalein flavonoid) in this herb have been the subject of intensive study with regard to their anticancer effects and other health benefits. In Asia, Chinese skullcap is incorporated into a number of combination herbal products that have been used in adjunctive cancer treatment. I recently had the opportunity to review the literature published worldwide on this potentially important herbal agent, and have summarized it below in a clinically relevant format. I believe you will find the data quite intriguing and of great clinical importance.

### **General Features**

Chinese skullcap is a member of the mint family and grows in China and Russia.<sup>1,2</sup> Its root is a rich source of over 35 flavonoids, giving it a yellow color - hence its traditional name of golden root or *huang qin*, the Chinese term for yellow gold (known as *ogon* in Japanese).<sup>3,4</sup> One of the major flavonoids contained in the root of the plant is baicalin, a flavone glycoside (12percent-17percent of all skullcap root flavonoids), which yields the aglycone flavone baicalein, once hydrolyzed by gut bacteria.<sup>3</sup> Baicalein is readily absorbed into the bloodstream, where it has been shown to exert a broad spectrum of important biological activities.<sup>5</sup> Baicalein has been incorporated into a number of herbal combinations in TCM that treat a wide array of health conditions, including the widely used Asian herbal remedy, Sho-saiko-to.<sup>6,7</sup> Currently, baicalein is being studied for its anti-cancer, anti-inflammatory, antiviral, antibacterial and anti-allergy effects.<sup>8,9,10,11</sup> As explained below, its ability to halt the replication of various human cancer cell lines, via the inhibition of the 12 lipoxygenase enzyme system, is attracting a great deal of attention from the scientific community as a premiere agent in cancer research.

### **Clinical Application and Mechanism of Action: Anticancer Effects**

Many experimental studies indicate that baicalein (5,6,7-trihydroxyflavone) prevents and inhibits cancer growth via a number of direct and indirect physiological actions:

**a. Inhibition of 12-lipoxygenase enzyme and induction of apoptosis of cancer cells.** Baicalein has been shown to inhibit the 12-lipoxygenase enzyme, which converts arachidonic acid into a specific leukotriene (eicosanoid) required for cancer cells to proliferate. Studies demonstrate that by inhibiting the enzyme, baicalein inhibits cancer cell proliferation and induces apoptosis (programmed cell death) of human gastric cancer cell lines.<sup>12</sup> Further, activation of arachidonic acid by the enzyme has been shown to be critical for metastasis of human prostate cancer cells.

Experimental evidence demonstrates that after intraprostatic injection of mice with human prostate cancer cells, the cells pretreated with baicalein failed to metastasize to the lung and failed to express activity of the enzyme. This evidence suggests that in the presence of baicalein, various cancer cells can be prevented from multiplying and metastasizing to other tissues, and that a primary mechanism through which this occurs is via the inhibition of the enzyme.<sup>13</sup> The inhibition of cancer cell proliferation also lends itself to increased apoptosis and a better opportunity for immune cells to destroy tumor cells.<sup>12,13</sup>

Other studies testing baicalein as an antitumor agent have shown that it selectively induces apoptosis in human hepatoma cell lines (liver cancer cells) with minimal influence on noncancer cells.<sup>14,15,28,29</sup> Its ability to induce apoptosis is under intensive investigation; many studies provide evidence that it exhibits an extraordinary ability to selectively encourage apoptosis of many different human cancer cells. This is likely one of the primary ways in which it has been a useful addition to herbal combinations used in cancer treatment.<sup>16,17,18</sup>

**b. Antiproliferative effects:** Baicalein also has demonstrated anti-proliferative effects on human bladder cancer cell lines and a murine bladder cancer cell line, *in vitro*. In an *in vivo* experiment, mice were injected with bladder cancer cells with concurrent oral administration of a high-baicalein-yielding supplement in one group, or with no baicalein supplementation in the control group. All the control mice showed a progressive increase in tumor volume over the ensuing days of the study, whereas the mice treated with baicalein (*scutellaria*) showed a significant inhibition of tumor growth.<sup>19</sup>

In other experiments, baicalein has demonstrated antiproliferative effects on human pancreatic cancer cell lines and T lymphoid leukemia cells. The mechanism of action was shown to be through the reduction of protein tyrosine kinase activity and protein kinase C activity. Both of these enzyme activities are required

for normal cellular proliferation to occur. Thus, in addition to inhibiting the 12-lipoxygenase enzyme pathway and inducing apoptosis of cancer cells, baicalein is also known to reduce cancer cell proliferation by directly or indirectly inhibiting specific enzymes (protein tyrosine kinase and protein kinase C) required for cellular division and proliferation.<sup>28</sup>

**c. Antioxidant effects:** Baicalein is also a strong antioxidant and has been shown to protect DNA from undergoing cancerous mutations in challenge studies using potent carcinogens, such as benzo{a}pyrene, and toxins such as aflatoxin (AF)B.<sup>1,20,21</sup>

**d. Stimulation of DNA repair enzymes.** In vitro evidence indicates baicalein stimulates recombination and repair of damaged DNA, supporting its traditional inclusion in cancer formulas, and suggesting possible use after sunburn and radiation damage.<sup>22</sup>

**e. Inhibition of the 5 alpha-reductase enzyme.** Baicalein has been shown to inhibit the 5 alpha-reductase enzyme, which converts testosterone to dihydrotestosterone (DHT), strongly associated with the development of prostate enlargement (benign prostatic hyperplasia) and prostate cancer. As such, it is reported to be potentially useful for the prevention and/or treatment of androgen-dependent (testosterone-driven) disorders, including prostate enlargement and prostate cancer.<sup>23</sup>

### **Human Studies Involving Prostate Cancer Patients**

Human studies have primarily involved patients with advanced prostate cancer who were shown to be unresponsive to traditional medical drugs and other interventions. In a study performed by researchers from the University of California at San Francisco and Memorial Sloan-Kettering Cancer Center in New York, an herbal combination containing baicalein was administered orally to metastatic prostate cancer patients (previously unresponsive to standard treatments). It was shown to demonstrate reversal and/or stabilization of their condition - with significantly improved survival, quality-of-life scores and other positive outcomes in almost all patients.

After a median treatment period of 57 weeks, all patients with androgen-dependent cancer had a decline of 80 percent or more in their prostate-specific antigen (PSA) levels, undetectable in 81 percent of the subjects. In 31 of 32 patients, testosterone levels declined to that seen in castrated men. Nine men with elevated prostatic acid phosphatase levels (a marker for cancer progression) experienced declines of more than 50 percent. Of two patients with positive bone scans, one experienced a complete disappearance of cancerous

bone lesions, and the other showed improvement. One patient experienced a complete disappearance of a bladder mass, confirmed through a CT scan.

Of 35 patients with androgen-independent prostate cancer, 54 percent showed a drop in their PSA levels of 50 percent or more, and of 25 patients with metastasis to bone, two showed marked improvement; seven remained stable; 11 progressed; and five had no further bone scan follow-up, due to an increasing trend in their PSA levels.<sup>24</sup> Other studies involving men with known prostate cancer who were taking this herbal combination have demonstrated similar results. In a two-case report of hormone-refractory prostate cancer,<sup>25</sup> PSA levels dropped from 100ng/mL to 24, and from 386ng/mL to 114 within 16 months of supplementation. Studies following larger groups of men with prostate cancer for up to four years have also shown that this herbal formula significantly reduces PSA levels and improves survival and quality-of-life scores.<sup>26,27</sup>

Researchers attribute much of the antitumor effects of this herbal combination to the presence of baicalein. According to researchers, it has demonstrated impressive anticancer effects against androgen-dependent and androgen-independent human prostate cancer cell lines, and many of its anticancer mechanisms have been uncovered in recent years, through in vitro and in vivo experiments.<sup>16-18,24-28</sup> It appears to be of particular benefit in prostate cancer treatment, and in combination with other phytonutrients (plant-based nutrients) and micronutrients (vitamins and minerals), may help to prevent the development of clinically important prostate cancer, reducing prostate cancer incidence.<sup>26</sup> Animal studies indicate that baicalein may be effective in the treatment of other cancers as well, with experimental evidence supporting its potential use in stomach, pancreatic, bladder, liver<sup>12, 14, 15,19, 28</sup> and breast cancer.<sup>29-31</sup>

### **Hepatoma and Leukemia Patients**

Based on its traditional use and the documentation of its antitumor effects against various human cancer cell lines, baicalein has been used recently by doctors in Asia as a complementary supplemental agent in the treatment of hepatomas and leukemia in human subjects.<sup>29</sup>

### **Clinical Application and Mechanism of Action: Antiviral/Anti-HIV Effects**

In experimental studies, baicalein has been shown to inhibit the activity of the HIV-1 integrase enzyme, essential to the life cycle of the human immunodeficiency virus (HIV). This enzyme is responsible for catalyzing the insertion of the viral genome into the host cell chromosome. It is an attractive target for the

design of an HIV antiviral drug, because the integrase enzyme has no human counterpart.<sup>32</sup> In a review of all herbal medicines frequently used as alternative medical therapies by HIV-positive and acquired immune deficiency syndrome (AIDS) patients, J.A. Wu, et al., emphasized that experimental data suggest that baicalein inhibits infectivity and replication of HIV, and shows great promise as an important component to be included in herbal remedies used for HIV treatment.<sup>33</sup>

### **Effects on Asthma and Allergy**

Baicalein inhibits type I and II hypersensitivity reactions, confirming its traditional use in asthma<sup>34,35</sup> and allergic dermatitis.<sup>3</sup>

### **Anti-Inflammatory Effects**

Baicalein has shown impressive anti-inflammatory effects that appear to be mediated via repression of leukotriene B4 (inhibition of the 5-lipoxygenase enzyme), inhibition of interleukin-1B, and prostaglandin E2. Studies reveal it may be of benefit in the treatment of gingivitis (gum inflammation).<sup>29,36,37</sup>

### **Effects on Alzheimer's and Dementia**

In a rat model, baicalein has been shown to prevent the buildup of amyloid beta peptide (abeta), known to generate free-radical damage to brain cells and participate to a significant degree in the development and progression of Alzheimer's disease. Additionally, chronic inflammation occurs in Alzheimer's pathogenesis, and baicalein was shown to inhibit the 12-lipoxygenase enzyme responsible for brain inflammation, to a large degree. When tested against other known 12-lipoxygenase inhibitor agents, only baicalein was able to attenuate both nerve cell death (apoptosis) and the overexpression of abeta production. As such, it may help to prevent or forestall the development of Alzheimer's disease by reducing the buildup of abeta and inflammatory mediators, preventing brain cell death, which has been shown to be triggered by the accumulation of abeta in affected brain cells.<sup>38</sup>

In studies using human neuroblastoma cells, the antioxidant properties of baicalein were shown to inhibit free-radical damage to these nerve cells induced by treatment with hydrogen peroxide (a powerful free-radical generating agent). The researchers argue that oxidative (free-radical) stress plays an important role in the development of neurodegenerative diseases (e.g., Alzheimer's disease, multiple sclerosis, Parkinson's disease) and that antioxidants such as baicalein and quercetin (also a flavonoid) may be useful bioactive agents in the prevention and/or management of these conditions, pending further studies. Both

have shown impressive protective effects under experimental conditions.<sup>39</sup>

### **Inhibition of Xanthine Oxidase (Gout)**

Baicalein is one of few bioactive agents shown to inhibit the enzyme xanthine oxidase, responsible for the conversion of hypoxanthine to xanthine to uric acid, in the pathway for degradation of purines in the body. High levels of uric acid are a hallmark feature of gout and thus, baicalein supplementation may be an effective complementary intervention in the long-term management of this condition.<sup>40</sup> Allopurinol is a xanthine oxidase inhibitor, and a primary medication prescribed for the treatment of gout.

### **Dosage**

**Therapeutic purposes:** The usual doses, for therapeutic purposes, range from 150-200 mg per day of Baicalein.<sup>6</sup>

**General wellness:** Consider 50-100mg per day.

### **Toxicity and Adverse Side Effects**

Baicalein supplementation at therapeutic doses appears to be safe, with no reports of significant side-effects or toxicity. Baicalein or Chinese skullcap is not known to be contraindicated for any health conditions.<sup>41,42</sup>

### **Drug-Nutrient Interaction**

There are no known drug-nutrient interactions for baicalein or Chinese skullcap.<sup>42</sup>

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